

# CLINICAL PROCEEDINGS

*of the*  
CHILDREN'S HOSPITAL

WASHINGTON, D. C.

*November 1949*

VOLUME V

NUMBER 12



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# CLINICAL PROCEEDINGS

## OF THE CHILDRENS HOSPITAL

13th and W Streets, Washington 9, D. C.

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Published monthly by the Staff. Cases are selected from the weekly conferences held each Sunday morning at 11:00 A.M., from the Clinico-pathological conferences held every other Tuesday afternoon at 1:00 P.M., and from the monthly Staff meetings.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is \$1.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," The Children's Hospital, Washington, D. C. Please notify on change of address.

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Entered as second class matter November 21, 1946 at the post office at Washington, D.C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

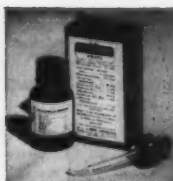
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# THE USE OF AEROSPORIN (POLYMYXIN B) IN SPECIFIC AND NON-SPECIFIC ENTERITIS IN INFANTS AND CHILDREN\*

## *A Special Report*

Sidney Ross, M. D.  
Frederic G. Burke, M. D.  
E. Clarence Rice, M. D.  
Harold Bischoff, M. D.  
John A. Washington, M. D.

In 1946, while conducting a systematic antibiotic screening of soil bacteria, Ainsworth<sup>(1)</sup> isolated a bacterium from the soil which was found to produce a new antibiotic highly active against gram-negative organisms. The organism was identified as *Bacillus aerosporus*, a gram-positive, aerobic, spore bearing rod and the antibiotic was originally designated as aerosporin. In July 1947, Stanely et al<sup>(2)</sup> described another antibiotic produced by *Bacillus polymyxa* which was called polymyxin. Various antibiotics have been derived from *Bacillus polymyxa* and have been designated as polymyxin A, polymyxin B, polymyxin C, and polymyxin D. All members of the polymyxin group are principally basic polypeptides plus a fatty acid component. Aerosporin (polymyxin B) differs from the polymyxin originally isolated by Stanely in that it contains phenylalanine and does not contain d-serine in the polypeptide linkage.

Aerosporin has been found to possess a high degree of bacteriocidal specificity against gram-negative organisms in vitro. The bacterial spectrum of aerosporin was found to show a lesser range than that of streptomycin; however, among the organisms sensitive to both drugs, Brownlee and Bushby<sup>(3)</sup> have demonstrated that aerosporin is ten to many hundreds of times more active than streptomycin and was found to have the additional important advantage in vitro of producing no aerosporin-resistant strains of organisms.

In view of the demonstrated efficacy of aerosporin against organisms of the coliform group in vitro, it was considered of interest to use the drug in a clinical trial in cases of specific and non-specific gastro-enteritis in infants and children. During the summer of 1948 a total of forty cases were treated with the drug. The types of cases are summarized as follows:

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\* Reprinted from "The Medical Annals of the District of Columbia," September 1949 with the permission of Mr. Theodore Wiprud.

Disease	Number of cases
Non-specific enteritis . . . . .	18
Shigella enteritis . . . . .	16
Salmonella enteritis . . . . .	4
Typhoid fever . . . . .	2
Total . . . . .	40

Representative case reports and a brief résumé of the efficacy of the drug in each group of cases are discussed below.

A series of eighteen cases of gastro-enteritis of non-specific origin in infants and children were treated with aerosporin. The drug was administered orally in a dosage of 2 mgms. per kilogram of body weight every four hours for periods ranging from four to ten days. No intramuscular aerosporin was used in this group. The average duration of therapy was 7.2 days. The organisms encountered on stool culture prior to therapy usually included *E. coli*, *Paracolon bacillus*, *Proteus morgagni* and *vulgaris*, *Pseudomonas aeruginosa*, and *Streptococcus fecalis*. Within forty-eight to seventy-two hours after initiation of aerosporin orally there was a noticeable inhibition of the stool bacterial flora which persisted throughout the course of therapy. Within two to four days after the drug was discontinued, the normal intestinal flora was once again in evidence on stool cultures. Very few of the stool cultures obtained while the patient was receiving aerosporin showed complete inhibition of the coliform intestinal organisms. It was very interesting to note that *Proteus* (*morgagni* or *vulgaris*) was the predominating organism and in many stool cultures was the sole organism remaining after aerosporin was given orally. This is to be compared with the phenomenon observed after oral administration of streptomycin where often the only organism which survived the coliform inhibiting activity of the drug was *Pseudomonas aeruginosa*.

In the eighteen cases of non-specific gastro-enteritis treated with oral aerosporin, we were unable to detect any salutary effect either with respect to the duration or the severity of the diarrhea. This opinion is predicated on the fact that during the past eighteen months, we have been specifically studying the effects of chemotherapeutic agents and antibiotics in both specific and non-specific gastro-enteritis and thus far have managed approximately 400 cases of diarrhea under this program at Children's Hospital. During this time we have run a parallel control series of patients who were managed in the conventional manner without any drug therapy. A comparison of the course of the diarrhea in infants receiving aerosporin with alternate cases receiving no drug therapy indicated that no singular difference in course of the disease was apparent. The evaluation of any therapeutic agent in non-specific diarrhea is extremely difficult at best and is

especially susceptible to abortive claims of therapeutic efficacy of one mode of therapy or another. In this regard, we are at variance with Brownlee and Bushby<sup>(2)</sup> who reported a series of fifty cases of non-specific diarrhea treated with aerosporin with "extremely encouraging results."

#### *Aerosporin in Shigella Enteritis*

There were sixteen cases of specific dysentery treated with aerosporin orally. The ages of the children ranged from five months to eight years. As for specific etiology, ten cases belonged to the Sonnei group while in the other six patients, a Flexner organism was isolated.

At least two positive stool cultures were obtained prior to initiation of therapy. During treatment daily stool cultures were obtained until the patients were discharged from the hospital. The media used included Salmonella-Shigella (SS) agar, desoxycholate citrate agar and tetrathionate broth. The rectal swab technique was used and all stool cultures were seeded simultaneously on these three media.

Aerosporin was administered by the oral route exclusively in all patients. The dose most commonly employed was 3 mgm. per kilogram of body weight every four hours. The daily dose of aerosporin ranged from 18 to 60 mgm. The duration of treatment varied from seven to fifteen days with an average of 10.6 days per patient. The sensitivity of the organisms encountered in this series varied from .02 to .08 micrograms per ml.

A series of consecutive negative stool cultures ranging from seven to twelve (average ten) was obtained before the patient was discharged from the hospital. Once the stool became negative for shigellae on aerosporin therapy, no cultural reversals were noted during the hospital stay.

In fourteen of the sixteen cases, a bacteriological cure was observed and in these cases the stool became negative for *Shigella* organisms within one to four days after starting aerosporin; the average time required for sterilization of the bowel was 1.2 days. Clinically the improvement was commensurate with the salutary effect observed bacteriologically. In two cases, however (#1 and #7), the stools remained positive for *Shigella* throughout the first week of therapy and after what was considered a fair therapeutic trial, the drug was discontinued. Both of these cases subsequently cleared up rapidly on oral streptomycin. It is interesting to note that in spite of the failure of the drug to effect a bacteriological cure in these two patients, the organism showed no increase in aerosporin resistance during the course of therapy.

It was our impression that aerosporin affected the course of the disease favorably in the majority of cases both clinically and bacteriologically. However, a comparison between this drug and streptomycin or sulfadiazine in *Shigella* enteritis revealed that aerosporin was somewhat less effective

than either of the two latter drugs. It could, however, be used to advantage in cases of shigella enteritis where the organism was found to be resistant to both streptomycin and sulfadiazine.

#### *Aerosporin in Salmonella Enteritis*

Salmonella infections like those due to *E. typhosa* have shown a singular refractoriness to antibiotic therapy up to now. During the past year, eight cases of salmonella enteritis at Children's Hospital were treated with large doses of streptomycin<sup>(4)</sup>. In spite of the demonstrated susceptibility of the salmonella organism to streptomycin in each case, seven out of eight patients showed only a transitory sterilization of the stool culture with a recurrence of positive cultures within three to eight days after streptomycin was discontinued. Because of the disappointing results with streptomycin and in view of the sensitivity of salmonella to aerosporin, the latter drug was given a therapeutic trial in four cases of salmonella enteritis in infants. In the first two patients, *Salmonella meunchen* was isolated; in the third case *Salmonella manhattan*, and in the fourth case *Salmonella anatum* was cultured. The aerosporin sensitivity of these organisms varied from .06 to .01 micrograms per ml.

Aerosporin was given both orally and intramuscularly to all four patients. The oral dose was 3 mgm. per kilogram of body weight every four hours and the intramuscular dose was .5 mgm. per kilogram every four hours. With this dosage schedule, spot blood levels taken during the course of therapy ranged from 1.4 to 4.2 micrograms per ml. Thus the aerosporin blood level exceeded the sensitivity of the organism by twenty to fiftyfold.

The results of therapy were varied. In case #1, a toxic reaction characterized by fever, malaise, and albuminuria occurred within two days after aerosporin was started and hence the drug was discontinued prematurely before its efficacy against the pathogen could be evaluated. A second trial on aerosporin ten days later produced a similar toxic reaction in this patient and was again discontinued after three days. In case #2, the stool cultures became negative within four days after aerosporin was started and ten consecutive daily cultures were similarly negative for salmonella during the course of the child's stay in the hospital. The drug was administered for nine days during which time a total of 1.5 grams orally and .45 grams intramuscularly had been given. A follow-up stool culture one month later was also negative. In case #3, the stool cultures were sterile within two days after aerosporin was started and seven consecutive cultures were negative during the next eight days in the hospital. The drug was discontinued on the tenth day during which time the child had received 1.9 grams orally and .24 grams intramuscularly. However, within five days after aerosporin was discontinued, the stool once again became positive for salmonella.

There was no increase in aerosporin resistance when the pathogen reappeared in the stools after termination of therapy. Thus the failure of aerosporin in this case can hardly be explained on the basis of acquired resistance of the organism. In case #4, a severe toxic reaction including fever, diarrhea, malaise, and albuminuria occurred within two days after the drug was started and aerosporin was discontinued on the third day before its efficacy against the infection could be evaluated.

In summary, only two patients out of the four received the drug long enough to evaluate its efficacy in salmonella enteritis. One of the two cases showed a bacteriological cure with the organism being absent from the stools during what was considered an adequate follow-up period. In the other fully treated case, a definite inhibitory effect on both the salmonella organisms and the normal stool flora was observed during the period of drug administration; however, the pathogen reappeared in the stools within five days after discontinuation of the drug. In the other two cases, premature discontinuation of therapy due to toxic reactions precluded any evaluation of the virtues of aerosporin in salmonella enteritis.

#### *Aerosporin in Typhoid Fever*

Brownlee and Bushby<sup>(3)</sup> have demonstrated that *S. typhi* (Rawlings strain) is inhibited by aerosporin in a concentration of .08 micrograms per ml. while the same strain is inhibited by streptomycin in a concentration of 16 micrograms per ml. Thus aerosporin was 200 fold more active than streptomycin against this organism. Because of the inefficacy of streptomycin therapy in typhoid fever as well as the demonstrated susceptibility of the organism in vitro to aerosporin, it was considered of interest to test the value of the latter drug in typhoid fever. Two cases of typhoid fever were treated with aerosporin. A summary of one of the cases is presented below.

S. H., a twenty-three month old colored female was admitted to Children's Hospital on August 9, 1948 with the complaints of fever and anorexia of one week's duration.

The child had been in good health until seven days prior to admission at which time she began to run a temperature elevation and shortly thereafter refused her feedings. The fever continued ranging between 101°F. and three days after the onset, she was seen by her local physician. Three intramuscular injections of 300,000 units of penicillin in oil and beeswax were given on consecutive days but there was no perceptible clinical improvement nor defervescence of temperature; hospitalization was therefore advised. Past history and family history were non-contributory.

A second case of typhoid fever, treated first with aureomycin and then with aerosporin yielded discouraging results. In both cases, the typhoid

organism was extremely susceptible to aerosporin in vitro ranging from .02 to .04 micrograms per ml.

The aerosporin blood levels in both cases ranged from 1.2 to 1.4 micrograms per ml.; thus the blood concentration was approximately 50 times greater than the sensitivity of the organism. Yet, there was no striking clinical effect resulting from the administration of aerosporin in either case. In case #1, the duration of the fever was eighteen days while in case #2, the child ran a spiking temperature for twenty-one days in spite of therapy. Both patients remained acutely ill during the entire period of therapy and followed the same course and duration of illness which characterizes the average untreated case of typhoid fever in the pediatric age group. It might be said that the bacteriological response in both cases was somewhat more encouraging than the clinical response.

#### TOXICITY OF AEROSPORIN

It has been shown that various members of the polymyxin group possess a renal damage factor (R. D. F.) which produces albuminuria of variable degrees. However, it has been claimed that aerosporin (polymyxin B) is the only member of the polymyxin group which may be used in man without danger of renal damage<sup>(3)</sup>.

In view of the fact that no precise data have as yet been reported on the toxicity status of aerosporin, the patients in our series were carefully observed clinically and pertinent laboratory examinations were performed during the course of therapy including daily urinalyses and frequent blood non-protein nitrogen determinations to ascertain whether any evidence of renal toxicity intervened.

#### *Toxicity after Intramuscular Administration*

As will be noted in chart #2, the majority of toxic reactions occurred after intramuscular administration of the drug. In twelve cases who received the drug intramuscularly\* local tenderness and pain at the site of injection were observed in every patient. This was ameliorated slightly when 1 per cent novocaine was added to the diluent. Malaise and anorexia were noted in one-half of the patients in varying degrees. A rise in temperature ranging from 99.5°F. to 101°F. occurred in two-thirds of the children during the course of intramuscular administration of the drug. The fever usually appeared on the second day after aerosporin was started and continued as long as the drug was given. Blood non-protein nitrogen determinations were obtained both before, during, and after administration of the antibiotic.

\* Six of these cases were selected from the ward at random and received the drug experimentally, while the other six patients were given aerosporin intramuscularly for a specific infection.

Using 40 mgm. % as the upper limit of normal, a slight increase was noted in 41 per cent of the cases. In no instance, however, did the non-protein nitrogen go above 50 mgm. % and usually within two to four day after cessation of the drug, the non-protein nitrogen had returned to normal. Albuminuria (ranging from 15 mgm. % to 200 mgm. %) was observed in one-third of the cases while casts and white cells were noted in 75 per cent of patients. It is well to emphasize, however, that in the majority of instances, only a portion of the daily urinalyses performed on each patient showed any albumin, white cells or casts during the course of therapy. In all instances, the urinary findings substantially disappeared within two to four days after termination of aerosporin. Leukocytosis ranging from 12,000 to 19,000 white blood cells was noted in 50 per cent of the cases. There seemed to be a positive correlation between the incidence of leukocytosis and the appearance of a febrile reaction in the same patient. An eosinophilia (varying from 6 per cent to 20 per cent) occurred in 16 per cent of the patients. No other changes in the differential count nor in the red cell count were observed.

#### *Toxicity after Oral Administration*

After oral administration of aerosporin, fewer evidences of toxicity were noted in the thirty-four cases observed. This is predicated on the fact that little of the drug is absorbed from the intestinal tract. Spot blood levels taken during oral administration showed no detectable aerosporin titer; however, it is well to point out that with the assay method used in our study, the least amount of aerosporin detectable was an amount equivalent to the sensitivity of the *E. coli* test organism, i.e., 0.3 to 0.5 micrograms. One would suspect by inference that small amounts of the drug have been absorbed after the drug was given orally since 33 per cent of the patients showed an increase in non-protein nitrogen during therapy; in one case, the non-protein nitrogen rose to 60 mgm. % and in another it went up to 64 mgm. %. In all instances, a normal non-protein nitrogen was again observed within two to four days after oral aerosporin was discontinued. In contrast to the high incidence after intramuscular administration, only a small number of patients showed transitory albuminuria and microscopic urinary changes after taking the drug orally. Eosinophilia was noted in 12 per cent. No fever, malaise or anorexia occurred with the oral aerosporin.

The following case summary illustrates well the nature of the renotoxic manifestations after aerosporin administration:

*E. E.*, a nine month old colored male infant, was admitted to Children's Hospital on July 31, 1948 with a history of fever and diarrhea of five days' duration.

The patient had been in good health until the onset of the present illness at which time he began to pass five to seven watery green stools a day. Concomitantly, the

infant began to run a fever and appeared somewhat drowsy and anorexic. The stools remained watery and frequent and continued to have a diarrheal consistency during the next five days at which time, hospitalization was advised. No blood or mucous was noted at any time. One week prior to the onset of diarrhea, the infant was taken for a visit to a rural section of Maryland and had been given unboiled well water. Past history and family history were not contributory.

Physical examination revealed a well developed, moderately dehydrated infant who appeared acutely ill. The temperature was 104°F. The skin was hot and dry with some loss of tissue turgor. The eyeballs were sunken and anterior fontanelle was depressed. The respiratory excursions were suggestive of a moderate acidosis. The physical examination was otherwise not remarkable.

Laboratory examination revealed a hemoglobin of 9 gm. with 4.14 million red cells; the white cell count was 13,500 with 49 per cent neutrophils, 48 per cent lymphocytes, 2 per cent basophils, and 1 per cent monocytes. Urinalysis was negative. Using the copper sulfate falling drop method, the hematocrit was found to be 25 while the specific gravity of blood was 1.047 and specific gravity of plasma 1.030. A carbon dioxide combining power on admission was 27 volumes per cent. Examination of the spinal fluid was negative. A stool culture was positive for *Salmonella* (group C<sub>2</sub>) in our laboratory and final identification of the organism by the use of group specific O sera showed it to be *Salmonella meunchen*.\*

Initial treatment consisted of vigorous parenteral fluid administration including  $\frac{1}{4}$  M lactate, 5 per cent glucose in water, saline, plasma, and whole blood. Oral alimentation was withheld for the first forty-eight hours and then gradually resumed in graded progressive fashion. The initial formula was a weak dilution of powdered protein milk.

During the first two days in the hospital, the temperature fluctuated between 104°F. and 105°F. The diarrhea persisted and the infant remained acutely ill. On the following day, the temperature dropped rapidly. When the results of the stool cultures became known on the third day, the patient was started on aerosporin (polymyxin B). This dose was 20 mgm. orally and 6 mgm. intramuscularly every four hours. Daily urinalyses, blood non-protein nitrogen determinations, and stool cultures were obtained during the administration of aerosporin.

Within eighteen hours after initiation of aerosporin therapy, the temperature rose sharply to 103°F. and the infant appeared unduly fretful and somewhat drowsy. A urinalysis obtained on the day after aerosporin was started showed many white cells. Blood non-protein nitrogen determinations during this time ranged between 23 and 34 mgm. %. Daily stool cultures remained positive for *Salmonella meunchen*.

In view of the febrile reaction and the urinary changes, both of which were considered to be untoward effects of the drug, aerosporin was discontinued after forty-eight hours. Within twelve hours, the temperature dropped precipitously to normal and the infant appeared to be less toxic clinically. Daily urine examinations during the next week showed a disappearance of the albuminuria while a few to a moderate number of white cells were still noted in each urine on microscopic examination of the sediment. The infant's clinical condition had improved considerably during this time and the diarrhea had subsided. However, daily stool cultures still remained positive for *salmonella meunchen*.

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\* We are indebted to Dr. L. R. Kuhn of the Army Medical Center, Washington, D. C. for confirmation and final identification of the organism by the use of group specific O sera.

In view of our previous disappointing results with other forms of therapy in *Salmonella enteritis* (including streptomycin), it was decided to try aerosporin once more under continued close supervision. Thus on August 12, aerosporin was started again; the dose was 20 mgm. orally and 4 mgm. intramuscularly every four hours. Within thirty-six hours, the temperature rose again, this time to 101°F. Similarly the albuminuria reappeared and showed 200 mgm. and 90 mgm. respectively on August 13 and 14. There was concomitantly a slight increase in the number of white cells in the urine. No azotemia was noted. On the third day of drug administration, the stool culture became sterile. However, in view of the recurrence of the untoward reaction, aerosporin was discontinued after three days. On the following day, the stool culture again showed a reappearance of *Salmonella meunchen* and daily cultures remained positive thereafter. The albuminuria disappeared within forty-eight hours after aerosporin was discontinued, and similarly the white cells in the urine were no longer in evidence.

The toxic manifestations of aerosporin may be due to impurities such as histamine-like and pyrogenic factors which may decrease or completely disappear when a pure form of the drug is obtainable. On the other hand, the untoward side reactions of aerosporin noted in our series may be intrinsic to the drug itself. It would be our impression, however, that the high incidence of toxic reactions especially after intramuscular administration would preclude its widespread usefulness in its present state of purity.

#### CONCLUSIONS

1. Aerosporin, a new antibiotic, derived from *Bacillus aerosporus* was given a clinical trial in forty cases of non-specific and specific enteritis in the pediatric age group.

2. The drug was found to be quite effective orally in cases of shigella enteritis. In typhoid fever and non-specific gastro-enteritis, little if any salutary effect from aerosporin was observed. The results in salmonella enteritis were equivocal.

3. A high incidence of toxic manifestations from the drug was observed, especially after intramuscular administration. Untoward side reactions included local pain and tenderness at the site of injection, fever, malaise, leukocytosis, eosinophilia, and evidence of renal damage characterized by albuminuria, microscopic urinary findings and azotemia. These toxic reactions would preclude its widespread usefulness.

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## HENOC'S NON-THROMBOPENIC PURPURA WITH A REVIEW OF THE LITERATURE

*Case Report No. 164*

John P. McGovern, M.D.  
John R. Conley, M.D.

B. F. 49-7709

B. F., a ten year old white male was admitted to the Children's Hospital on June 20, 1949 with a chief complaint of "rash on the legs" of three days' duration. The boy had been well until ten days before admission when he developed sore throat and slight fever. He received one 5,000 U. penicillin troche and the next day seemed much improved. Except for intermittent epigastric pain and associated vomiting, he was asymptomatic and played in his normal fashion until three days before admission. At that time he had a fever of 103°F. and over the buttocks a rash was noted which by description was petechial in character. The next day the individual lesions had increased in size and new lesions were noted over both lower extremities. There was now swelling of the feet and ankles so that he was unable to put on his shoes. The attending physician made no definite diagnosis, but empirically prescribed an unknown amount of benadryl and aureomycin every four hours which the patient consistently vomited. The fever subsided, but the epigastric pain, vomiting, and rash persisted until admission.

The family history, past history, and the review of systems were essentially non-contributory, there being no history in either the patient or his family of asthma, hay fever, exzema, or any other allergic manifestations. It was noted in the past history, however, that one year ago the child received X-ray therapy by a dermatologist for "recurrent herpes simplex" of the face.

The pertinent physical findings at the time of admission revealed a well developed and fairly well nourished young white male lying quietly in bed in no apparent acute or chronic distress. Over the skin of the buttocks and lower extremities numerous small flat purpuric lesions were noted. Scattered petechiae were observed on the soles of the feet, the upper extremities; several on the face, and one was noted in the conjunctiva of the right eye. In the peri-anal region and gluteal folds of the buttocks, there were approximately twenty hard, raised, non-pigmented verruciform lesions varying in size from one to three millimeters in diameter. Microscopic examination revealed these to be typical of *molluscum contagiosum*. There were numerous markedly advanced dental caries. The abdomen was soft and flat with slight epigastric tenderness to deep palpation. There were no masses nor could the

liver or spleen be palpated. The remainder of the physical examination was not relevant.

The accessory clinical findings on the day of admission were: hemoglobin, 14 grams; red blood cells, 1,900,000; white blood cells, 11,400; and platelet count, 220,000 per cubic millimeter (Reese-Ecker method). The urinalysis was negative except for the presence of acetone. The Kahn and Mazzini tests for syphilis were negative. The sedimentation rate by the Wintrobe method was corrected to thirty millimeters per hour. A blood culture revealed four colonies per cubic centimeter of hemolytic *Staphylococcus aureus*. This was thought to be a contaminant as six repeated blood cultures were sterile. The agglutination tests for typhoid "O" and "H", paratyphoid A and B, proteus OX<sub>19</sub>, and brucellosis were negative.

During the first ten days of his stay in the hospital he continued to complain of almost constant, rather severe, epigastric pain associated with intermittent bouts of vomiting. A benzidine test on the vomitus was positive for occult blood. During the first six days he had one to three soft tarry stools each day that were positive for occult blood, but on the seventh day he developed a severe diarrhea which consisted of fifteen black liquid stools. No pathogens could be isolated from these stools. The following day there were fourteen bowel movements, the stools being similar in character to those of the previous day except that they now contained bright red blood. At this time the bleeding, clot retraction, coagulation, and prothrombin times were all within normal limits. The erythrocyte fragility test, blood civatimic acid level, and platelet counts were also within normal limits. Several Rumpel-Leeds tests for capillary fragility were negative. The platelet count at this time was 230,000. All of these tests were negative when repeated on numerous occasions.

The purpuric spots had almost disappeared by the third hospital day, but on the next day, numerous fresh, raised purpuric spots had appeared over the buttocks. These remained in evidence for about seven days. On the tenth hospital day he had a generalized convulsion lasting about fifteen minutes which was followed by a semi-comatose period lasting about eight hours. His recovery was rapid and there were no neurological residuals following this episode. Except for anorexia the patient was asymptomatic during the next two days, but on the thirteenth hospital day he again complained of abdominal pain, vomited several times, and began having tarry stools. Two days later a new crop of purpuric lesions appeared on the buttocks and by the next morning much of the lower extremities was involved. These purpuric lesions were somewhat different from those seen and described on the previous occasions, as they were now urticarial in nature with an erythematous area around the periphery (see fig. 1). None of these

lesions extended above the waist. On the sixteenth hospital day he received seventy-five milligrams of Protamine (Lilly) and on the following day received fifty milligrams in 500 ml. of normal saline. Proctoscopic examination, complete upper and lower barium studies of the gastro-intestinal tract, and intravenous pyelography revealed no abnormalities.

He remained asymptomatic until the twenty-fourth hospital day when it was revealed that he ate some licorice candy at about noon time. Six hours later, twenty to thirty purpuric spots were noted over the legs and buttocks. On further questioning the patient, it was found that he had



FIG. 1. B. F. Photograph to illustrate the type and distribution of the purpuric lesions.

eaten some of the same brand of candy just prior to the onset of the previous crop of lesions. In retrospect it was also noted that he had had aspirin preceeding both of these last two episodes. Five days later all petechiae had disappeared, and at this time intradermal skin tests and passive transfer tests were done for foods and inhalents. All of these were negative. The patient was also tested for gum arabic (the only common allergenic substance found to be in the licorice candy), chicle, karoya, and tragacanth. These tests also were negative. Later he was fed a portion of the same licorice candy and in five hours a small fresh crop of petechiae was noted

over the legs. Three days following this, the child was given five grains of aspirin which was also followed in six hours by numerous new petechiae over the legs. He was discharged after forty days in the hospital to be followed in the allergy clinic.

#### DISCUSSION

Under the general heading of "anaphylactoid purpura," the form of non-thrombopenic purpura represented by this case is usually associated with the names of Schönlein and Henoch. A perusal of the available literature, however, reveals that according to Osler<sup>(1)</sup>, Willan<sup>(2)</sup> was the first to describe a case of purpura associated with abdominal colic, vomiting, bloody diarrhea, painful and swollen joints, and a variety of skin lesions including purpura, urticarial wheals and angioneurotic edema. Under the name of "peliosis rheumatica" the joint symptoms were emphasized by Schönlein<sup>(3)</sup>. Henoch's contributions consisted chiefly of stressing the gastro-intestinal complications and of attempting to demonstrate this condition as a distinct clinical entity.

Although many theories have been advanced, it seems fair to state that the etiology of this symptom-complex remains an enigma. Osler<sup>(6, 7)</sup> wrote that he believed the skin manifestations, abdominal crisis, and joint involvement to be due to a single pathological process, and later<sup>(8)</sup> called attention to the similarity of the purpuric areas in this disease to allergic phenomena such as urticarial wheals and areas of angioneurotic edema. Glanzmann<sup>(9)</sup> suggested the term "anaphylactoid" purpura and felt that the necessary foreign protein was derived from bacterial infection. Specific food allergy has been described as the etiologic agent in numerous papers<sup>(10, 11, 12, 13)</sup>. Goldstein<sup>(14)</sup> enumerates the following possible factors: 1) Anaphylatoxin associated with a bacterial protein; 2) food allergy; 3) histamine or histamin-like substances. In a case observed by one of us<sup>(15)</sup>, paroxysmal diarrhea, urticaria, and signs of vasomotor collapse were elicited on exposure to sudden decreases in temperature. The urticarial response to the application of ice in this patient could not be controlled with benadryl hydrochloride. With the use of capillariscopes, Müller<sup>(16)</sup> observed the skin capillaries in a case of Schönlein-Henoch's purpura to be dilated, lengthened, and partially distorted. When all the facts are considered, it is difficult to escape the conclusion that this entity is on the basis of a vasomotor disturbance possibly as the result of an allergic hypersensitivity.

The clinical syndrome of Henoch's purpura is protean in its manifestations with the mode of onset being quite variable. Frequently it begins with malaise, anorexia, and a mild pyrexia, but severe cramplike abdominal pain accompanied by vomiting may usher in the attack. Albuminuria and hematuria may occur with the onset or at any time during the attack. The

skin lesions do not usually appear until one to several days later, and because of this fact, there is often considerable confusion as to the diagnosis. The clinical picture may simulate appendicitis, intussusception, Meckel's diverticulum and peritonitis, and failure to make a correct diagnosis has led to useless laparotomies<sup>(17, 18, 19)</sup>. However, it should be kept in mind that surgery is sometimes indicated as intussusception<sup>(20, 21, 22)</sup> does occur rarely as a complication of the bowel pathology. It is suggested<sup>(23, 24)</sup> that roentgenological studies of the small intestine may be of diagnostic aid in the obscure abdominal cases. Signs of meningeal irritation with xanthochromic cerebro-spinal fluid has been reported<sup>(25)</sup>.

Schönlein-Henoch's purpura may be differentiated from purpura hemorrhagica on the basis of the following comparisons (after Goldstein).

	Schönlein-Henoch	Purpura Hemorrhagica
Constitutional symptoms:	Malaise, headache, anorexia, coated tongue, fever	Few; no fever unless secondarily as result of complicating infection or profound anemia
Special features:	Urticaria, erythema, edema, joint pains and swelling; abdominal colic, vomiting, melena, hemorrhagic nephritis	Absent; melena without colic and hematuria without nephritis do occur
Skin lesions:	Petechiae, purpura, urticaria, erythema	Ecchymosis, extensive sugillations, purpura
Localization:	Extremities preferred especially near the joints; head usually spared	Irregular, frequently on head
Mucous membrane hemorrhages:	Moderate bleeding from gastrointestinal tract, otherwise rare	Frequent epistaxis, stomatorrhagia, uterine, vesical, gastro-intestinal and renal bleeding may be extensive
Bleeding time:	Normal	Increased
Clotting time:	Normal	Normal
Clot:	Retractile	Non-retractile
Morphology of blood:	Slight leukocytosis; occasional eosinophilia	Tendency to leukopenia and relative lymphocytosis
Platelets:	Generally normal, may be increased or moderately diminished	Marked thrombopenia with giant forms
Tourniquet test	Positive	Very strongly positive with large ecchymoses

#### SUMMARY

1. A case of Henoch's purpura is presented.
2. Evidence is given that specific allergens might have been of etiologic significance.

3. The symptom-complex is discussed from its historical, etiologic, and diagnostic standpoints.

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THE CLINICAL PROCEEDINGS OF THE CHILDREN'S HOSPITAL is indebted to: E. L. Bowersox, E. V. Brumfiel, E. M. Finstad, J. C. Hawley, A. G. Jelalian, G. T. Knoll, J. V. Loughran, D. J. McCrossan, R. F. Powell, K. A. Randall, Dr. David Fitzgibbon, Lt. E. Turner, Tabulating Machines Division, Remington Rand, Inc., and H. H. Goodman for their recent gift made in the name of Jimmy Boykin who is a convalescent from a recent automobile accident. This gift will be used to improve the character of this magazine.

We are sincerely grateful.

## A CASE OF SMOKE INHALATION

*Case Report No. 165*

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G. H. 47-12661

G. H., an eighteen months old colored male, was admitted to Children's Hospital on March 8, 1949, after being rescued from a smoke-filled room in which a fire of undetermined origin had occurred. The child was crying when removed from the room and had not been overcome by the smoke.

The past history revealed no previous hospitalization or serious illnesses. The patient had been vaccinated for small-pox and immunized against diphtheria, pertussis, and tetanus. His physical and mental development had apparently been normal. The family history was non-contributory.

On admission, the patient appeared to be a well developed and well nourished male, standing in bed, quite restless, with a frequent croup-like cough. The blood pressure was 105/70; pulse, 136; respirations, 28; and temperature, 99.4°F. There were first degree burns of the forehead, anterior chest above the nipples, the entire right upper extremity, and the lateral aspect of the left upper extremity. First and second degree burns were present on the cheeks, tips of nose and ears, and below the umbilicus almost to the inguinal region. A large area of second degree burns was present between the umbilicus and the nipples. The remainder of the body was not burned. There was slight inflammation of the nasal mucosa and the pharynx.

The respirations were of a grunting character, and the patient had a croup-like cry when disturbed. Rhonchi and medium moist rales were heard throughout the entire lung fields, more so in the left upper chest posteriorly. The liver was felt 2.5 centimeters below the right costal margin. There was slight distension of the abdomen. The rest of the examination was negative.

Admission laboratory tests revealed a hemoglobin of 11 grams, an erythrocyte count of 3,800,000, a leukocyte count of 9,000 with 71 per cent neutrophils and 29 per cent lymphocytes, and a negative sickle cell preparation.

The patient was immediately placed in an oxygen tent on admission, and a debridement of the large second degree burn area was done. Rayon and furacin dressings and pressure bandages were applied to the burned areas. Aqueous penicillin in a dosage of 50,000 units intramuscularly every three hours was begun. One injection of procaine penicillin, 300,000 units, was given intramuscularly. The child was given clear liquids orally. Blood pressure, pulse, respiration, and temperature were recorded every hour for the first twelve hours, the interval being gradually increased to every four hours.

The condition of the patient remained about the same during the day. The blood pressure ranged from 80/50 to 120/60, the pulse from 110 to 140, the respirations from 28 to 35. The temperature, however, rose to 101°F. The child did not appear to be in shock, nor did he have acute respiratory distress. The respirations, however, were noisy at times. A tap water enema and aspirin were given for temperature of 102.4°F. at 4:00 a.m. on the morning of March 9, 1949. During the day, the patient began to take fluids better by mouth and by noon, the temperature was 99.8°F. Laboratory examination revealed a hemoglobin of 12 grams, erythrocyte count of 4,100,000, leukocyte count of 12,500 with 72 per cent neutrophils, sedimentation rate of 20 mm. per hour, hematocrit of 42 mm., and 6.39 grams of serum proteins. In view of the fact that the patient had pulmonary edema and no evidence of shock or hemoconcentration, no fluids or plasma were given intravenously. Mucous had to be aspirated from the mouth and trachea frequently. The chest findings remained the same.

At 4:00 p.m., the blood pressure increased to 160/100, the pulse was 150, and the respiratory rate was 36. By midnight the pulse rate was 160; the respirations, 38; and the blood pressure, 120/90. The patient was very restless from 1:00 a.m. to 5:00 a.m. on the morning of March 10, 1949. At approximately 6:00 a.m. the child became cyanotic and had labored respirations. Much thick, yellow mucous was aspirated from the trachea and the color improved. At 8:20 a.m. the color of the skin and mucous membranes was normal. There was some rib retraction with respirations, but there seemed to be a good air exchange. Medium moist rales were still present over the entire chest. However, the patient remained alert and did not seem to be in distress at this time.

About twenty minutes later, however, the patient suddenly began to gasp for breath and became cyanotic. He had practically no air exchange. The mouth was held rigidly shut and could not be forced open. Tubing was passed through the nostrils in an attempt to aspirate the trachea. Coramine was given subcutaneously. After the jaws relaxed slightly, they were forced open and an airway inserted. Aspiration was attempted by passing the tubing through the airway. Intracardiac coramine was given in an unsuccessful attempt to stimulate the heart which had stopped beating. The patient was pronounced dead at 8:50 a.m.

Necropsy was performed thirty-six hours after death. Examination revealed the body of a well developed and well nourished colored male child with the areas of burns described in the clinical history. There was moderate lividity of the dependant parts but no obvious cyanosis. The serous cavities did not contain fluid. The thymus gland weighed 20 grams but it did not impinge on the surrounding structures. The veins entering the right heart, the right auricle and ventricle, the pulmonary veins, and the left auricle were dilated and filled with unclotted blood. The heart otherwise was nor-

mal. The mucosa of the trachea and bronchi was injected. From the region of the bifurcation of the trachea and extending into the large and smaller bronchi of both lungs, there was thick whitish-yellow mucous which almost formed a cast of the structures containing it. On gross inspection, all lobes of the lungs were emphysematous and they were twice the normal weight. There was marked emphysema, atelectasis of the lower lobes and portions of the upper lobes, with the remainder of the lung tissue congested. The liver, spleen, and kidneys showed moderate congestion.

Microscopic examination of the lungs showed many areas of peribronchial infiltration with round cells and polymorphonuclear cells. The cellular infiltration extended into the surrounding alveoli. These alveoli and others also, contained erythrocytes. The walls of many of the alveoli were congested and infiltrated with leukocytes. Many bronchi and bronchioles contained cellular elements, debris, and mucoid material with some bronchi almost completely filled. The mucosa of the bronchioles was disrupted. Areas of atelectasis were present.

In summary, the primary pathologic picture was one of tracheobronchitis with obstruction, bronchopneumonia, and alveolitis. The extent of the bronchial obstruction with mucoid material caused respiratory embarrassment and subsequent overloading of the right heart. An acute inflammatory process in the alveoli and bronchi also contributed to the cause of death.

#### DISCUSSION

In a review of the literature on smoke inhalation only eight references on the subject could be found, four of which were from the Boston Coconut Grove Disaster.

The staff of the Massachusetts General Hospital treated 114 patients following the Coconut Grove fire. Of these, 39 were admitted and 7 died of respiratory complications within twelve to sixty-two hours after the fire. The staff of the hospital recognized three stages in smoke inhalation.

(1) *Excitement stage*: The patients were hyperactive either because of pain or hysteria. For pain, a small dose of morphine was the drug of choice. This was given intravenously rather than intramuscularly if the patient was in peripheral vascular collapse to prevent the absorption of more than one dose and its respiratory depression when the peripheral circulation was restored.

For hysteria, Nembutal intravenously was used. Paraldehyde was not so good because of the pulmonary irritation incurred in its elimination.

If the hyperactivity was due to anoxia, an adequate airway had to be established either by aspiration, tracheotomy, or intubation and the administration of oxygen.

(2) *Edematous stage*: This stage occurred usually about twenty-four hours

after exposure, but in three of their cases, the onset of this stage was as early as three hours after exposure to the smoke and flames.

These patients became cyanotic, dyspneic, restless and the chest became full of moist rales. Laryngeal examination showed burns, redness, and marked edema.

In this stage, tracheotomy or laryngeal intubation must be considered. Saline was not used at any time because of the increased pulmonary edema and exudate incurred. Intravenous fluids of any type had to be given with care.

(3) *Bronchiolitic stage*: This stage occurred at a varying period with constriction of the bronchioles, focal atelectasis, and localized lobular collapse especially at the base. Frequently, an associated emphysema was seen at the apices. These patients usually did well if secondary pneumonia was prevented.

There were six post-mortem examinations performed at the Massachusetts General Hospital on victims of this fire. Three of these patients were dead on arrival and three died after forty to sixty-two hours in the hospital.

The three who were dead on arrival all showed:

1. Generalized cutaneous burns.
2. A cherry red discoloration of the skin and organs of a varying degree indicative of carbon-monoxide poisoning.
3. A severe non-necrotizing hemorrhagic tracheitis and bronchitis.
4. Acute massive pulmonary edema.
5. A sero-hemorrhagic exudation of the upper tracheo-bronchial tree with no leukocytic reaction.

In all these cases the mechanism of death was due to anoxemia on the basis of: carbon-monoxide poisoning, pulmonary edema, and possibly the action of other poisons such as oxides of nitrogen.

Of the three cases that died in the hospital, all showed:

1. A severe diffuse hemorrhagic focal membranous reaction in the trachea, bronchi, and bronchioles.
2. Areas of necrosis and membrane throughout the respiratory tree.

Two of the cases showed a severe necrotizing laryngitis with a pseudodiphtheritic membrane and almost complete laryngeal stenosis.

In the pulmonary parenchyma, there were three different pathological pictures.

1. One case showed only massive acute pulmonary edema.
2. One showed massive atelectasis with large areas of hemorrhage into the atelectatic alveoli.
3. The other showed widely disseminated focal atelectasis and compensatory emphysema.

A case reported from the University Hospital, Ann Arbor, Michigan

demonstrates the stages excellently. The patient was a sixty-seven year old white female who was admitted to the hospital sixteen hours after being exposed to smoke and flames for thirty minutes. On being rescued, the patient was incoherent and irrational. She showed second degree burns of the face, neck, and forearms, and was coughing up soot stained mucous. Examination at the time of rescue revealed rales at the left base and axilla. The patient was given morphine sulfate  $\frac{1}{4}$  gr. subcutaneously and within three hours her lungs were clear; the patient was rational and her blood pressure was normal. This was an example of the excitement phase.

About nine hours after being rescued, she began to have coughing paroxysms, productive of muco-purulent sputum and her chest was full of rales. The patient was taken to the hospital.

On admission her temperature was 99.5°F.; pulse, 105; respiration, 20; blood pressure, 100/60. The patient spoke hoarsely and laryngeal examination revealed a purulent exudate and edema of the arytenoid cartilages. Physical examination showed decreased resonance of both lung fields with patchy medium coarse rales throughout both lung fields. X-ray of the chest showed patchy areas of increased density and increased broncho-vascular markings.

The patient was put on penicillin, low salt diet, ammonium chloride, and atropine sulfate. Twenty-four hours after admission (forty hours after patient was exposed to fire), the temperature rose suddenly to 105°F. Pulse went to 150 and the respirations to 45. The patient began to have labored breathing; the respirations became wet and rasping, and she became markedly cyanotic. The patient was treated with oxygen and repeated aspirations, and symptoms cleared in forty-eight hours. This was the edematous stage. The bronchiolitic stage was demonstrated two months later when the patient was bronchoscoped revealing cicatricial narrowing of all branch bronchi. X-ray of the chest at this time revealed areas of atelectasis. This patient while being followed had two bouts of broncho-pneumonia a frequent complication in this stage.

Therefore, in the management of these patients the treatment is in four phases.

1. *Sedation* to prevent or reduce shock to a minimum.
2. *Preservation of an adequate airway*, by aspirations, tracheotomy, or laryngeal intubation to insure adequate respiratory exchange of air.
3. *Oxygen* to decrease anoxia by:
  - a. Increasing the partial pressure of oxygen which increased the transfer through the altered pulmonary membranes.
  - b. Hastening the dissolution of carboxyhemoglobin.
4. *Antibiotics* to decrease the chances of a superimposed pneumonia on an already damaged lung.

The brother and sister of the patient admitted here at Children's Hospital were victims of the same fire. Their ages were  $3\frac{1}{2}$  years and 5 months respectively. They were overcome with smoke, being comatose when rescued. On admission, they had regained consciousness, and neither was severely burned. Both were found to have pulmonary edema. Each had thick, yellow mucous present in the trachea during the first seventy-two hours following admission. They received the same treatment as G. H. and both recovered.

Tracheotomy was considered for the patient on the second day, but was not done since it was thought that the pathology extended into the bronchi. However, aspiration of the respiratory tree might have been carried out more successfully by way of a tracheotomy.

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## CLINICAL-PATHOLOGICAL CONFERENCE

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Assisted by: William Crowell, M.D.

Francis J. Troendle, M.D.

By Invitation: John O. Nestor, M.D.

Francis J. Troendle, M.D.

G. M. 40-7153 A

A two months old colored male was admitted to Children's Hospital because of anorexia, vomiting, and irritability. The patient had a normal birth at Freedman's Hospital. During the eighth month of the mother's pregnancy, it was found that she had a positive Wassermann and she was started on anti-luetic therapy. The mother had six children by a previous marriage, the oldest being fifteen and the youngest seven years of age. The siblings were in good health. The father's serology was negative.

The patient was apparently well until about one week before admission, at which time, he was seen on the out patient department. He was feverish and he was treated with sodium bicarbonate for pyelitis. No urine was obtained for examination.

The admission physical examination revealed a pale colored infant weighing two pounds more than his birth weight (7 pounds 8 ounces). The fontanelle was bulging and the neck was moderately stiff. The patient had puffy eyelids. A loud apical systolic murmur was heard, and the abdomen was distended. There were no palpable abdominal masses or organs. The Neurological was negative. No lymphadenopathy was present.

The admission laboratory work disclosed an erythrocyte count of 3,000,000 with 9 grams of hemoglobin. The leukocyte count was 10,000 with 36 per cent neutrophiles, 62 per cent lymphocytes, and 2 per cent monocytes. Urinalysis was normal. The spinal fluid contained 340 cells per cubic millimeter with 85 per cent polymorphonuclears. Sugar was 40 milligrams per cent and protein was 30 milligrams per cent. No organisms were found on smear or culture. A repeat hemogram after admission showed a hemoglobin of 7.5 grams with 2,200,000 red blood cells and 17,200 white blood cells. The differential showed 16 per cent neutrophiles (12 per cent segmented, 3 per cent bands, and 1 per cent young forms), 34 per cent lymphocytes, 7 per cent polymorphocytes, 2 per cent lymphoblasts, 1 per cent monocytes, 38 per cent small mononuclear cells of the lymphoid type, and 2 per cent unclassified. The thrombocyte count was 40,000 and the red cells showed marked achromia and microcytosis.

The Roentgen examination revealed the lung fields to be clear. The long bones showed changes suggestive of rickets and repeated examinations of the bony skeleton were done. They revealed definite evidences of periosti-

tis and metaphysitis of all the bones of both upper and lower extremities without involvement of the epiphyses. There was involvement of the tenth and twelfth thoracic and first lumbar vertebrae. The ribs appeared moth eaten. The skull did not seem to be involved. It was the examiner's impression that the long bone changes suggested syphilis as the etiological factor, but that a blood dyscrasia should be considered.

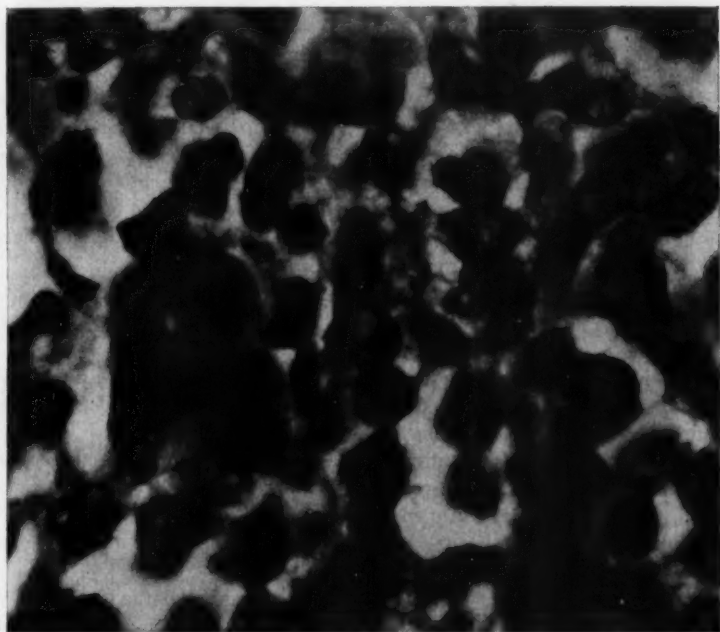


FIG. 1. Section of liver showing some normal liver tissue and the pale staining reticulo-endothelial cells characteristic of Letterer-Siwe's disease.  $\times 1275$ .

The blood chemistry including calcium, phosphorous, and non-protein nitrogen was within normal limits. Repeated Kahn and Wassermann tests were negative. The tuberculin skin test was negative. The patient ran a very stormy course with a gradual decrease in weight from 10 pounds to 7 pounds 5 ounces on the forty-third day. His anemia persisted despite frequent transfusions, and his hemoglobin had dropped to 3.5 grams on the twenty-eighth hospital day. The red blood cell count was 1,400,000; the white blood count was 8,600, and the differential was similar to the one described above, with many immature forms. The thrombocytopenia per-

sisted. The temperature was low grade in type varying between 100°F. and 102°F. Death occurred on the forty-third day of hospitalization.

#### DISCUSSION

*John O. Nestor, M.D.:* The fact that the mother had one positive Wassermann and then was started on antiluetic therapy forces us to assume that both she and the child were luetics even though it is poor policy to make a diagnosis of syphilis on the basis of a laboratory test. The fact that none of the other siblings showed evidence of lues plus the fact that the father's serology was negative, casts considerable doubt on this diagnosis.

Fever, tenderness in the flank, and crying upon urination does not necessarily make the diagnosis of a urinary infection because other conditions can cause these symptoms. Certainly a urinalysis should have been done. The fact that no urinalysis was performed and the statement that the child was treated for pyelitis with sodium bicarbonate force me to conclude that this child was admitted several years ago, because that sort of diagnosis and treatment has not been the practice here in recent times.

The child weighed 9½ pounds on admission, which is only about a pound under average for a two months old child. This would seem to indicate that the history of an illness of only a few days was correct.

The fever, irritability, vomiting, stiff neck, and bulging fontanelle all point to central nervous system pathology and the subsequent spinal tap confirmed this as we will discuss later.

Unfortunately, the heart murmur was not described more accurately as to location, radiation, and harshness. If it were localized at the apex, it would not be indicative of any specific congenital defect. I assume it was a functional murmur and that the heart was normal, especially in the absence of cyanosis.

One wonders if some of the abdominal organs were enlarged, or if possibly tumor masses were present but because of the abdominal distension could not be felt.

The absence of significant lymphadenopathy is perplexing because all of the possible diagnoses we have in mind are usually accompanied by considerable lymphadenopathy either generalized or localized.

The normal urinalysis on admission fairly well rules out a urinary infection. The blood count on admission revealed only a moderate anemia but the repeat count showing anemia, leukocytosis, thrombocytopenia, and the presence of many young forms is certainly suggestive of a leukemia. Dr. Troendle informs me that a peroxidase stain was not done to differentiate between the myeloid and lymphoid series. The evidence is strong enough to cause us to add leukemia to syphilis as one of the possible diagnoses. The question arises as to whether or not this blood picture might be

a response to severe anemia or infection. Ordinarily, the young forms have cleared from the normal infant's blood by the time he is two weeks of age. The large number of young forms and the thrombocytopenia would seem to indicate that infection was not the prime reason, but perhaps a contributing factor. The presence of so many young forms also rules out an aplastic or hyperplastic anemia.

The spinal fluid findings force us to consider central nervous system lues, tuberculosis or pyogenic meningitis, encephalitis, and leukemic infiltration. The high proportion of neutrophiles would be against the diagnosis of lues or tuberculosis. The normal sugar level would certainly be against the diagnosis of lues or tuberculosis. The normal sugar level would certainly be against the diagnosis of tuberculous meningitis or any other pyogenic meningitis. The cells are not reported to be abnormal in any way, and this would be against leukemic infiltration. Encephalitis would not explain the rest of the picture, especially the bone changes.

The periostitis and metaphysitis immediately suggest several possibilities. First is lues because of the positive serology in the mother and bone changes at the early age of two months. Both rickets and scurvy must be considered, but it is very early for either of them to be manifested by bone changes and the generalized changes are not typical of either. Neuroblastoma is a possibility, but there is no palpable abdominal tumor and the bone changes of a metastasizing neuroblastoma are usually localized and unilateral although occasionally generalized bilateral symmetrical involvement such as this does occur. Leukemia is a definite possibility also.

The normal blood calcium, phosphorus and non-protein nitrogen do not help us much and a blood phosphatase apparently was not done. The repeatedly negative Wassermann and Kahn tests throw considerable doubt on the diagnosis of syphilis but do not eliminate it.

In conclusion, I feel that I cannot make a definite diagnosis with the information available but merely list the main possibilities in the order of probability. They are:

1. Leukemia, acute lymphatic
2. Syphilis
3. Neuroblastoma with metastasis.

In all probability it is a combination of leukemia and infection—probably syphilis.

*Dr. Herbert Glick:* Was a blood culture made? It seems to me that an infection must be considered. I would suspect a pyelonephritis. How would you explain the presence of the 340 cells per cubic millimeter in the spinal fluid?

*Dr. Nestor:* I believe that the increased cell count in the spinal fluid could have been caused by syphilitic involvement of the meninges.

*Dr. Bennett Olshaker:* I do not believe that syphilis would account for the thrombocytopenia.

*Question from the Floor:* Could tuberculosis account for this patient's blood count?

*Dr. Nestor:* I am inclined to believe that netative skin test ruled out that disease.

*Question from the Floor:* How do you explain the negative Wassermann in the child?

*Dr. Nestor:* I do not believe that one can rely on the serology before the third month.

A vote was taken with the following diagnoses being favored by those present.

Leukemia.....	9
Syphilis.....	6
Leukemia and syphilis.....	3
Neuroblastoma.....	2
Genito-urinary anomaly and infection.....	1

#### PATHOLOGIC DISCUSSION

*E. Clarence Rice, M.D.:* The body was that of a well developed and moderately well nourished colored male infant weighing 3.24 kgm.

Examination of the skeletal system revealed cancellous enlargement of the lower pole of the right frontal bone, enlargement of the costochondral junctions of the ribs and osteoporosis involving the tenth and twelfth thoracic vertebrae.

The thymus was atrophic and the bronchial and mediastinal lymph nodes appeared to be normal, however, the mesenteric and retroperitoneal lymph nodes were enlarged and the latter group were quite adherent to the tissues about the aorta. On section they had a homogeneous appearance indicative of replacement of the normal structures.

The serous cavities were free of fluid or adhesions.

The heart and lungs were grossly normal.

The liver weighed 210 grams and extended 2.2 cm. below the costal margin in the right mid-clavicular line. The tissue was purplish-red and firm. The surface was elevated rather generally by numerous firm grayish-red nodules, varying in size between 1-15 mm. in diameter. These extended throughout the organ and on the surface a number had an umbilicated appearance.

The spleen weighed 16 grams, was of a purple color and free of any nodules or evidence of pathological change.

The genito-urinary system was grossly normal.

There was no definite evidence of syphilis.

The anatomical diagnoses made on the basis of the gross findings were:

1. Leukemic infiltration of the liver, mesenteric and retroperitoneal lymph nodes.
2. Osteochondritis of the ribs.
3. Osteoporosis of the right frontal bone and the tenth and twelfth thoracic vertebrae.

Microscopically, it was found that the changes noted in the liver, lymph nodes, and bones all represented areas of cells of the reticulo-endothelial system. These varied considerably in size. Some were no larger than lymphocytes; others had large diameters. These areas had no inflammatory reaction zone about them. In the lymph nodes, the above mentioned cells completely replaced the normal lymphoid architecture; and a number of eosinophiles were present. In the liver, the adjacent tissue was relatively normal. The germinal centers of the spleen showed marked increase in the reticulo-endothelial cells.

As Doctor Nestor suspected, this patient died a number of years ago. A number of pathologists who examined the sections at that time made the following diagnoses:

1. Lymphoblastoma
2. Hodgkin's disease
3. Endothelioma

In recent years these sections have been re-examined and the unanimous opinion of the pathologists is non-lipoid histiocytosis (reticulo-endotheliosis or Letterer-Siwe's disease).

During the past twenty years, there has been an accumulation of information concerning certain granulomatous lesions and reticulo-endothelial hyperplasias of bone. At present it is believed by many that the three diseases: Hand-Schüller-Christian disease, Letterer-Siwe's disease, and eosinophilic granuloma of bone are related to each other. Frequently it will be noted that the findings ordinarily associated with two of the above diseases are found in the same patient. This evident overlapping has helped to crystallize the thought that the three diseases can be considered as a group.

Reticulo-endotheliosis or Letterer-Siwe's disease, which was the disease that affected this patient is a relatively rapidly progressing disease affecting the bones, liver, spleen, lymph nodes and other lymphoid organs. Usually, it is seen in infants and children and ordinarily runs a fatal course. Histologically there is a predominance of histiocytes which replace the normal lymphoid structures. There is considerable variation in the size of these cells and the number of their nuclei. Lipoid is ordinarily absent; eosinophiles may be present.

The placing of the three diseases: Letterer-Siwe's, eosinophilic granuloma,

and Hand-Schüller-Christian in one group and taking the latter out of the category of the primary disorders of lipoid metabolism marks a change in medical thought which has made itself evident during the past nine years.

Although the blood and gross findings were suggestive of leukemia, the histopathology was not consistent with this disease. The usual evidences of syphilis did not manifest themselves grossly or microscopically.

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